

# Surfactant Protein D as a Novel Therapy for Periventricular Leukomalacia: Is It the Missing Piece of the Puzzle?

Defne Engür<sup>†</sup> and Abdullah Kumral<sup>\*,‡</sup>

<sup>†</sup>Neonatology Department, Adnan Menderes University, Aydın, Turkey

<sup>‡</sup>Neonatology Department, Dokuz Eylül University, İzmir, Turkey

**ABSTRACT:** Activation of microglia with an inflammatory insult, which plays a central role in periventricular leukomalacia (PVL), results in premyelinating oligodendrocyte death via release of certain cytokines, reactive oxygen and nitrogen species. Toll-like receptor (TLR) 4 is necessary for lipopolysaccharide (LPS) induced oligodendrocyte injury in the CNS. Having an ability to bind TLR 2, 4, and LPS receptor CD14, surfactant protein D (spD) may be a promising agent to counteract the pathways associated with PVL. Supplementation of surfactant treatment with spD may be the key point in prevention of PVL by suppression of inflammation and preventing damage to pre-OLs in a vulnerable premature brain operating through TLRs.

**KEYWORDS:** Periventricular leukomalacia, inflammation, toll-like receptor, surfactant protein D

Periventricular leukomalacia (PVL) is a distinct type of brain injury in premature infants, with a characteristic distribution.<sup>1</sup> Infection/inflammation and ischemia/reperfusion injuries are two mechanisms in the pathogenesis of PVL which operate in concert to potentiate each other.<sup>1</sup> Activation of microglia with an inflammatory insult which plays a central role in PVL, results in premyelinating oligodendrocyte (pre-OL) death via release of reactive oxygen, nitrogen species and cytokines.<sup>1</sup> It has been recently shown that toll-like receptor (TLR) 4 is necessary for lipopolysaccharide (LPS) induced oligodendrocyte injury in the CNS.<sup>2</sup> The number and density of microglial cells expressing TLR on their surface are found to be increased in premature infants.<sup>1</sup>

Mechanisms which modulate the individual inflammatory response acting via TLRs may change the severity of PVL. Surfactant protein D (spD) is an essential component of the innate immune system which orchestrates the inflammatory process by rapid resolution of inflammation.<sup>3</sup> Having an ability to bind TLR 2, 4, and LPS receptor CD14,<sup>3</sup> spD may be just the thing, promising to counteract the pathways associated with PVL. SpD enters circulation and is found in detectable amounts in human cord blood, but levels are low in premature babies as expected.<sup>4</sup> Commercial surfactant preparations do not contain spD; hence, they are deprived of beneficial immunomodulatory effects. Surfactant treatment for a premature infant will just provide a local effect associated with surface tension without any distant antiinflammatory action. Supplementation of surfactant treatment with spD may be the key point in prevention of PVL by suppression of inflammation and preventing damage to pre-OLs in a vulnerable premature brain operating through TLRs. Understanding the precise roles of surfactant proteins as components of the immune system will give us new insights into the pathogenesis and treatment of PVL.

## AUTHOR INFORMATION

### Notes

The authors declare no competing financial interest.

## REFERENCES

- (1) Volpe, J. J. *Neurology of the Newborn*, 5th ed., pp 359–379, WB Saunders, Philadelphia.
- (2) Lehnardt, S., Lachance, C., Patrizi, S., Lefebvre, S., Follett, P. L., Jensen, F. E., Rosenberg, P. A., Volpe, J. J., and Vartanian, T. (2002) The toll-like receptor TLR4 is necessary for lipopolysaccharide-induced oligodendrocyte injury in the CNS. *J. Neurosci.* 1 (22), 2478–2486.
- (3) Ohya, M., Nishitani, C., Sano, H., Yamada, C., Mitsuzawa, H., Shimizu, T., Saito, T., Smith, K., Crouch, E., and Kuroki, Y. (2006) Human pulmonary surfactant protein D binds the extracellular domains of toll-like receptors 2 and 4 through the carbohydrate recognition domain by a mechanism different from its binding to phosphatidylinositol and lipopolysaccharide. *Biochemistry* 18 (45), 8657–8664.
- (4) Dahl, M., Holmskov, U., Husby, S., and Juvonen, P. O. (2006) Surfactant protein D levels in umbilical cord blood and capillary blood of premature infants. The influence of perinatal factors. *Pediatr. Res.* 59, 806–810.

Received: November 23, 2012

Accepted: November 28, 2012

Published: December 19, 2012

